Study Title: Cluster randomised controlled trial of a complex intervention package to reduce blindness from severe microbial keratitis in Nepal

Participant Information Sheet and Consent Form: For enrolment into the clinical trial

Introduction

Thank you for taking time to hear about this study. You are being invited to take part in the early intervention clinical treatment trial for cornea infection. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read or listen to the following information carefully and to talk to others about the study if you wish. Ask us if there is anything that is not clear or if you would like more information. Do not sign the consent form unless you are satisfied with the answers to your questions and decide that you want to be part of this study. Take time to decide whether you wish to take part.

Why have I been invited?

You have been invited to take part because you have a problem with the clear part of the front of your eye, which is called the cornea. This is either a scratch (corneal abrasion) or an infection of the cornea (microbial keratitis).

What is this study about?

Infection of the cornea is an important cause of blindness. A scratch in the cornea allows infection to enter and an ulcer to begin. These infections can be very serious with some people losing the sight in the affected eye.

Different types of infectious organisms can cause corneal ulcers. These include bacteria and fungi. In tropical regions about half of all corneal ulcers are caused by fungi. Bacteria and fungi need to be treated with different types of eye drop medicines. Treatments for fungal eye infections are frequently not very effective, in addition access to these treatments in many countries is very limited and can be expensive.

Many people with corneal infection end up with poor vision or other eye problems because of delays in the infection being recognised and treatment being started. With this delay the condition becomes very severe, by which stage there is often nothing that can be done to save the vision or the eye itself.

This study is about testing out a new strategy in the primary health care setting to reduce the delay in diagnosis of cornea infection and the starting of an eye drop treatment, called chlorhexidine, that covers many different types of infections. They person with the infection would then be referred urgently to the regional eye hospital.

Chlorhexidine is an antiseptic. It is very effective at killing bacteria, fungi and other types of infectious organisms. It is used in medical care worldwide in several different ways. For example, it is used to clean skin before surgical operations, in antiseptic creams for skin cuts and as a mouth wash to prevent and treat mouth infections. It has been used in eye care for more than thirty years as an eye-drop preservative, for sterilizing contact lenses, for pre-operative topical antiseptic and for treating corneal infections.

If chlorohexidine eye drop were available at primary health care facilities, it would make this treatment much more easily accessible to many people with corneal infections and allow them to start appropriate treatment early in the course of the infection, as they proceed to an eye hospital to have a change of getting a good outcome.

This study will test if using this approach of an early intervention for people with corneal infection can reduce the risk of getting severe infections and blindness due to corneal infection.

Do I have to take part?
No. Your involvement is entirely voluntary. If you agree to take part, we will then ask you to sign a consent form. If you decide to join and change your mind, you are free to withdraw at any time without giving a reason. This will not affect the standard of care you receive. If you decide not to participate in the study, then you will be offered the standard treatment for your condition.

What will happen to me if I take part?
If you agree to be part of this study, the following will happen:

1) Baseline Assessment – In primary health centre:

- The health worker has already carefully examined your eyes thinks that you are eligible to join the study. We will ask you a few basic series of questions. This will include basic contact information, a short history of your current eye problem, and treatment you have had before arriving at the hospital.

- If have a corneal abrasion – a scratch without infection – the health worker will give you antibiotic eye ointment (called chloramphenicol) to tack three times each days for three days. You will be asked to come back after three days to re-check your affected eye.

- If you have a corneal infection you will be referred urgently to the Sagarmatha Choudhary Eye hospital, Lahan. We strongly encourage you to attend this referral as quickly as you are able to, in order to be fully checked for the type of infection and to start treatment to match it.

- In half of the health centres the health workers are also going to give people with cornea infection a bottle of chlorhexidine eye drops to be taken one drop every hour. To be started straight away when you are in the health centre. To continue taking this until you are seen in the Eye Unit in Lahan. In addition, we will send you reminder phone messages on the phone number that you have given us, to remind you to attend the eye clinic for additional treatment.

- In half of the health centres the health workers are also going to give people with cornea infection a bottle of chloramphenicol eye drops to be taken one drop every hour. To be started straight away when you are in the health centre. To continue taking this until you are seen in the Eye hospital at Lahan.

- As the risks to an unborn or breast-fed baby from eye drops use are unknown, pregnant and breastfeeding women will be excluded from participating in this study. They will be referred to the Eye hospital at Lahan for management.

2) Baseline Assessment – In Hospital Eye Clinic:
If you are referred to Sagarmatha Choudhary Eye Hospital, Lahan your contact details will be communicated to our team at Lahan who may contact you to provide additional guidance on your travel. On arrival at the clinic:

- We will ask you a series of questions. This will include basic demographic information, the history of your current eye problem, and treatment you have had before arriving at the hospital.

- We will then carefully examine both eyes using a special microscope.

- Your eyes will be photographed with a camera. This is additional to standard care, and will help us to monitor the infection and the response to treatment.

- We will use a special microscope to look at the cornea to see if we can find a fungal infection. This involves putting anaesthetic drops on the eye. A soft plastic device then gently touches the eye so to see if you have a fungal infection. This is additional to standard care, and will help us to find out the type of infection you have more rapidly so that we can offer you the most appropriate treatment.

- We will collect samples from the corneal ulcer to test in the laboratory to try to identify what is causing the infection. Anaesthetic eye drops will be used numb the eye so you will not feel anything while we collect the sample by brushing the surface.

- We will check your blood sugar level for diabetes. This is done using a finger-prick blood sample. If this is raised, we will refer you to a separate group of doctors to help you with this.

- We will collect a sample of the cells from the inside of your cheek by gently rubbing a swab for a few seconds. This is additional to the standard of care. The purpose is to try to understand how the body fights the infection and why some people develop this eye problem and others do not.

3) Treatment:

- Once the initial results of the tests for infection are available, the eye doctor will prescribe eye drop treatment that is appropriate to the infection type that is identified. If you were already started on chlorhexidine eye drops in the primary health centre you may be advised to continue taking these if there is evidence that they are working well.

- If your infection is severe, we may advise that you stay in hospital for daily review for the first few days. You will be treated with standard antibiotic or antifungal eye drops regularly for three weeks.

4) Follow-up Assessments:

- Initially, most people with corneal infections stay in hospital for several days so that the clinical team can monitor the response of the infection to the treatment.

- We would like to review the response to treatment and document the clinical findings at the following times after you start treatment: two days, 1 week, 2 weeks, 3 weeks, 2 months and 3 months.

- On each occasion we will ask you a few questions about your eye and the treatment. We will measure your eye sight. We will examine the eye with a microscope and photograph it with a camera.

- At 1 week, 2 weeks and 3 weeks we will repeat the *in vivo* confocal microscopy test that was done at your first assessment. This is done to see how the infection is responding to treatment. This involves putting anaesthetic drops on the eye so that you do not feel any discomfort. A soft plastic device then gently touches the surface of the eye so that we can take special photographs of the front of your eye (“scan”)

- At 1 week if you still have an open ulcer on the cornea we will repeat the sample collection to test for the ongoing presence of the infection. This involves first putting anaesthetic eye drops on the surface of the eye. Then gently scraping the surface of the corneal ulcer and testing for the presence of fungus and bacteria in the microbiology laboratory.

- Sometimes infections do not respond to the treatment. In such cases it may be necessary to alter the treatment or perform an operation. The eye doctors who will be looking after you will monitor your progress closely and advise you about further treatment might be needed.

- At three months, you will be contacted by a team from the Sagarmatha Choudhary Eye hospital at Lahan and invited to have your vision checked to determine how well your eyes can see.

- You may be withdrawn from the study without your consent if the researchers believe it is in your best interest or if you fail to follow study procedures.

What are the side effects or risks of taking part?

1. **It is important to recognise that corneal infection is a serious, sight threatening condition.** Many patients, whatever the treatment used, have reduced vision in the affected eye after it has resolved. In some people the affected eye will become blind. Sometimes the infection, despite lots of treatment, can progress to cause a hole to develop in the cornea (Perforation) and sometimes it is so severe it is necessary to perform an operation to remove the eye content.

2. **Local Irritation:** As with most eye drops, there is the risk of local irritation or stinging. This usually only lasts for a short time.

3. **Allergic Response:** Very rarely, eye drops can provoke a local allergic reaction on the surface of the eye or the eyelids.

4. **Pregnancy and Breast Feeding:** The risks to an unborn or breast-fed baby from these eye drops use are unknown. Therefore, pregnant and breastfeeding women are excluded from participating in this study.

5. **Chlorhexidine 0.2% eye drops:** Chlorhexidine eye drops are used on the surface of the eye as an antiseptic before procedures and also in the treatment of fungal and other eye infections. It has not been associated we any serious side effects. It may cause mild irritation and very rarely a local allergic response. This concentration of chlorhexidine is approved to be used in much larger volumes as a mouth wash. It is considered to be safe and is not associated with any systemic side effects.

6. **Unknown Risks:** The treatments in this study may have rare side effects that are currently not known. If during the course of the study new information becomes available, the researchers will share this with you.

What are the possible benefits of taking part?

- The study will involve tests for the type of infection. This helps the doctor looking after you to choose the best type of treatment for your eyes. These tests are not usually available for patients in Nepal.
- The costs for your clinical assessment, tests, treatment and transport to the follow-up visit (after you initially come to Lahan) will be paid for by the study.
- By participating in this study, you will be helping to answer the question about whether or not this early intervention programme can reduce the risk of sight loss in the affected eye.

What will happen to the clinical records, photographs and test results?

Your records will remain strictly confidential at all times. The information will be held in a secure office at your treating hospital. Only the people organizing or supervising the trial and regulatory authority auditors will have access to it. These include officials delegated by the Sponsor (London School of Hygiene and Tropical Medicine), the Nepal Health Research Council (NHRC), The Drug Development Administration (DDA) and trial Data Safety Monitoring Body (DSMB).

A study number rather than your name will be used on study records or the database wherever possible. Your name and other facts that might identify you will not appear when we present this study or publish its

results.

Your name will not be passed to anyone else outside the research team, unless we have your direct instruction to do so, for example to make a medical referral.

The photographs of the eye and the result of the laboratory test for infection will be shared with computer engineers to help develop a programme that can automatically analyse the image to see if this can provide some indication of the cause of the infection. Images of corneal infection may also be used for educational and teaching purposes, including in publications. All personal identifying information will be removed before sharing images.

What tests will we do on the sample?

The samples collected from the surface of your eye will be tested in several different ways to determine what is causing the infection. This work will be done in the hospital microbiology laboratory, where you are being treated. A portion of the infection sample will be transferred for additional special tests at KCMC Hospital Biotechnology (Tanzania), the London School of Hygiene and Tropical Medicine (UK) and Radboud University Nijmegen Medical Center (The Netherlands), as some of the tests will require additional special equipment that is not available at all sites.

- We will look for the type of infection using a microscope and by growing the organisms in the laboratory. We will test the organisms that grow to see which medicines work best to kill the infection, which is helpful in guiding the choice of treatment to be used.

- The swab samples from the ulcer will be used to test for infection using molecular diagnostic tests and to evaluate new tests that may be used to find the cause rapidly in the clinic.

- We will use study genetic material of the organism causing the infection to find out the exact type of infection and its ability to resist treatments. Samples from the ulcer may also be used to investigate your immune response to the infection, so that we can better understand what causes corneal scarring

- We will store a sample of the infection causing organism indefinitely for additional testing.

- The genetic material from the cells from your cheek will be sent to the UK or to KCMC Hospital in Tanzania. We would like to store it until a later time when a sufficiently large number of samples has been collected to conduct an analysis of this genetic material. The purpose would be to try to better understand how the human immune system fights the infection and why some people develop this eye problem and others do not. By doing these tests we hope that it will help us to develop approaches that will help to prevent or improve outcomes from this condition.

- As part of this consent we are asking that you give us permission to store this material to be able to test it at a later date as mentioned above. We do not know exactly for how long we shall store the genetic material before we have assembled a sufficiently large collection during the course of several planned studies to be able to proceed to the sample analysis, however, we anticipate a period of at least five years.

What will happen to the results of the research study?

The results of the study will be available after it finishes and will be included in peer reviewed medical and scientific journals and may be presented at medical meetings. Results will also be published on a publicly accessible trials database. The data will be anonymous and none of the patients involved in the trial will be

identified in any report or publication. Should you wish to see the results, or the publication, please ask your study doctor.

Who is funding the research?
The research is being funded as part of a grant from the Wellcome Trust, UK.

Who is organising the research?
It is being organised through a research partnership between the London School of Hygiene and Tropical, Sagarmatha Choudhary Eye Hospital, Lahan, Nepal.

What if relevant new information becomes available?
It is not anticipated that new information will become available during the course of this study. However, if it does, this will be shared with you by the researchers in case this affects whether you wish to continue in the study.

What if something goes wrong?
If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions. If you remain unhappy and wish to complain formally, you can do this through the head of the hospital eye department or the named person on the following page. The London School of Hygiene and Tropical Medicine holds insurance policies which apply to this study. If you experience harm or injury as a result of taking part in this study, you may be eligible to claim compensation.

Who has reviewed the study?
Prospective research such as this is looked at by an independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and approved by (1) London School of Hygiene and Tropical Medicine Research Ethics Committee; (2) NHRC; (3) DDA.

What will happen if I don't want to carry on with the study?
Your participation in this study is entirely voluntary. You may refuse to participate or may withdraw from this study at any time without penalty or loss of any rights or benefits to which you are otherwise entitled. The study doctor may also stop your participation in the study at any time for safety reasons. If you decide to withdraw from the study you should contact a member of the study team immediately. You do not have to give a reason when stopping, however for safety reasons, it is suggested that you tell the study doctor if you decide to stop because of an unwanted side effect. If you withdraw from the study, we will only use data collected before this decision, unless you request this to also be withdrawn. If you withdraw from the study, researchers, authorized persons from the Sponsor and the regulatory authorities will still require access to your medical notes to verify the data collected up to the date of your withdrawal.

Contact Details
Nepal Study Site: Dr. Reena Yadav, Sagarmatha Choudhary Eye Hospital, Lahan, Nepal email: reenapink@gmail.com, Phone +977-9808070069
Chief Investigator: Prof. Matthew Burton: T: +44 2076368636, email: matthew.burton@lshtm.ac.uk

You will be given a copy of the information sheet and a signed consent form to keep.
Thank you for considering taking the time to read this sheet.

Cluster randomised controlled trial of a complex intervention to prevent severe microbial keratitis

Consent Form No 1: Enrolment into the clinical trial

Participant Name_____ Study ID Number: _____

	Please initial box
1. I confirm that I have read and understand the participant information sheet dated ..... (version .....) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered fully.	
2. I understand that my participation is voluntary and I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	
3. I understand that sections of my medical notes and data collected during the study may be looked at by responsible individuals from the London School of Hygiene & Tropical Medicine, from national regulatory authorities or from this hospital, where it is relevant to my taking part in this research. I give permission for these individuals to access my records.	
4. I agree to take part in this clinical treatment trial.	
5. I agree to the collection, laboratory tests and storage for future analysis of the samples from the surface my eye infection to understand the disease as described above.	
6. I agree for the photographs of the front of my eye to be used in the publication or report released on the study, and for teaching purposes, including on the internet.	
7. I understand that data about/from me/the participant may be shared via a public data repository or by sharing directly with other researchers, and that I will not be identifiable from this information.	

Name of Participant *(printed)*	Signature/Thumbprint	Date
Name of Person taking consent	Signature	Date

The participant is unable to sign. As a witness, I confirm that all the information about the study was given and the participant consented to taking part.

Name of Impartial Witness *(if required)*	Signature	Date

1 copy for participant; 1 copy for Principal Investigator; 1 copy to be kept with hospital notes